

# Advances in Vaccine Technology And Their Impact on Managed Care

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## ABSTRACT

The discovery of vaccines has led to the near eradication of several important diseases and has had a tremendous impact on health for a relatively low cost. However, most vaccines in use today were developed by techniques that were pioneered more than 100 years ago and do not represent the full potential of the field. The introduction of genetic engineering has fueled rapid advances in vaccine technology and is now leading to the entry of new products in the marketplace.

In the past, options for the utilization of vaccines in the area of managed care had been quite limited because of the historically straightforward application of immunizations. The growing number and type of vaccine targets, coupled with novel, more effective formulations, adjuvants, and routes of delivery for vaccines, will undoubtedly create new challenges. Although progress in vaccine technology has the potential to prevent illness and reduce the economic burden of diseases in the long term, thereby improving outcomes, ongoing problems remain in the short term.

Who should and will pay for these anticipated improvements in health?

How will this period of change be managed?

This article describes the present “vaccine revolution” and attempts to answer these questions, which are becoming increasingly important in managed care.

**Key words:** vaccine, genetic engineering, technology, managed care, adjuvant

## INTRODUCTION

The advent of vaccines to prevent deadly childhood illnesses was one of the great success stories of the 20th century. Universal immunization against certain diseases has led to the eradication of smallpox and has almost completely eliminated many other infectious agents in the U.S., including those causing diphtheria, tetanus, poliomyelitis, measles, mumps, rubella, and *Haemophilus influenzae* type b invasive disease.<sup>1</sup> However, many other diseases, including the three biggest killers—human immunodeficiency virus (HIV) infection, tuberculosis, and malaria—have not yet been adequately targeted by a vaccine effective enough to achieve a similar outcome. In addition, some common vaccine-preventable diseases such as influenza and pertussis continue to cause significant morbidity and mortality, primarily in adults, because of the under-

utilization or ineffectiveness of available vaccines.<sup>2,3</sup>

Recent advances in vaccine technology stemming from the application of genetic engineering are now providing an opportunity to target new diseases. The previous century's successes in reducing the primary causes of mortality in childhood now include protecting against infectious agents that can result in significant morbidity. Scientific progress and these broadened applications will no doubt result in improved health-based outcomes, but progress often comes at a significant short-term cost. Although it is true that improved outcomes are the goal of health care technology and that preventing disease is preferable to treatment, thus reducing overall costs, confusion persists about the best course going forward.

Given the current underutilization of vaccines (even when patients have no copayments) and the expanding use of vaccines to cover morbidity rather than mortality, managed care organizations (MCOs) are confronted with several questions, particularly in terms of benefits, reimbursement, and formulary management. To accept the newer vaccine technology, MCOs will require not only improved mortality data but also cost-efficacy data with long-term proven outcomes accompanied by lower medical and pharmacy expenses.

For example, the use of new vaccines for human papillomavirus (HPV) must result in fewer cases of cervical cancer as well as in reduced cost savings in related medical expenses, such as for Pap smears and colposcopies. In this way, a manufacturer might be able to differentiate its product from a competing one. For several years, cost efficacy has been used to evaluate other classes of injectable vaccines, and it is a good method of comparing products when no head-to-head studies have been conducted. MCOs are beginning to analyze data involving comparisons of outlays for resources for specific outcomes, such as adverse events and hospitalizations.

## VACCINOLOGY: A RECENT HISTORY

Most vaccines in use today were developed by one of two classic methods. In the 19th century, Salmon and Smith pioneered the inactivation of an organism and the injection of immunogenic components.<sup>4</sup> The attenuation of live organisms, as first attempted by Louis Pasteur,<sup>5</sup> was adapted to modern vaccine technology by Enders et al. in the 1950s.<sup>6</sup> All but three vaccines in the currently recommended immunization schedule in the U.S.—those directed against hepatitis B virus, rotavirus, and HPV—are manufactured according to these techniques.

In the 1970s, a pair of key discoveries—the expression of proteins in plasmids and the ability to sequence DNA—ush-

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ered in the era of genetic engineering.<sup>7,8</sup> A decade later, in 1986, these techniques were used to develop the first *recombinant* vaccine, the hepatitis B vaccine.<sup>9</sup> Recombinant technology enables the target antigen to be produced outside the context of the parent organism, such that no live, infectious agents or potentially toxic components of those agents need to be handled. As a result, the quantity of antigen produced, the vaccine's safety, and the purity of the product are improved; efficacy is increased; costs are reduced; and potential side effects are minimized.

Since the advent of the hepatitis B vaccine in 1998, one recombinant vaccine, LYMERix, has been approved. Although LYMERix was effective against Lyme disease in adults,<sup>10</sup> Glaxo-SmithKline (GSK) withdrew this product in 2002 because of declining sales and negative publicity.<sup>11</sup> This outcome has dampened enthusiasm for further development of human vaccines against Lyme disease, but it has not had an adverse impact on the prospects for creating a vaccine that uses a similar strategy of a recombinant protein against other infectious agents. Many other recombinant vaccines are currently being evaluated in clinical trials to determine their activity against such varied targets as malaria, hookworm, cytomegalovirus, parvovirus, and anthrax.<sup>12</sup>

The second major advance in the 1980s was in the area of *adjuvantation*. Adjuvants are used to improve the presentation of an antigen to the immune system or to enhance its immunogenicity. The only adjuvants currently approved in the U.S. for the concomitant use with vaccines are the mineral salts calcium phosphate and alum.<sup>13</sup> Mineral salts are still used in some inactivated vaccines, but their effectiveness is modest at best.

For example, aluminum salts were included in early influenza vaccine formulations but were removed when the vaccines showed comparable immunogenicity in the absence of these salts.<sup>14</sup> In 1987, however, the application of conjugation as a method of adjuvantation led to the approval of a highly effective vaccine against *H. influenzae* type b, a leading cause of invasive infections, including meningitis, in children.<sup>15</sup>

Polysaccharide-based vaccines in general are poorly immunogenic, particularly in small children, because of a lack of T-cell help for the B-cell-dependent antibody response. Conjugating polysaccharides to a toxoid carrier converts these antigens from T-independent to T-dependent antigens, thus improving overall immunogenicity and lengthening the period of effectiveness.<sup>16</sup>

The success of this approach has led to the development of other polysaccharide conjugate vaccines, including Prevnar (Wyeth), a 7-valent pneumococcal conjugate vaccine approved in the U.S. in 2000, and Menactra (Sanofi-Pasteur), a quadrivalent meningococcal vaccine licensed in the U.S. in 2004. A vaccine directed against the serotypes of *Salmonella typhi*, which is responsible for typhoid fever, is now being studied.<sup>12</sup> The ongoing problem of suboptimal immunogenicity of protein-based vaccines, coupled with the success of conjugation for polysaccharide-based vaccines, is driving a search for new vaccine adjuvants.

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We predict that the development of virtually all vaccines licensed from this point forward will involve some form of gene-

tic engineering. Entire viral genomes can now be cloned into bacterial or yeast vectors, allowing manipulation of genes prior to "rescue," or regeneration of infectious organisms in culture. These techniques enable the rapid custom design of organisms for use in vaccines.

Influenza virus vaccines can serve as an example. The surface proteins from circulating strains can be cloned into plasmids and are co-expressed with a set of "backbone" genes responsible for high growth in eggs but attenuation in humans, allowing the production of safe, high-yield vaccines.<sup>17</sup> Undesirable traits, such as the multibasic cleavage site found in the main attachment protein of highly pathogenic avian influenza viruses, can be "edited out" at the DNA level before rescue of the virus, further enhancing safety.<sup>18</sup>

The use of plasmid-based methods also has the potential to hasten production of reassortant vaccines (i.e., vaccines from viruses created by combining genes from more than one organism or strain). The current process for making influenza vaccine relies on selecting appropriate vaccine strains from among many candidates generated by chance, whereas molecular methods allow complete control over the output, eliminating several steps in the generation of seed stocks.<sup>17</sup>

A variety of virus types, engineered by these methods to be safe in humans, are being used to express immunogenic foreign proteins outside of the context of the virulent parent organism. As an example, adenoviruses in which critical virulence genes are deleted have been used to express proteins from HIV<sup>19</sup> and are being utilized in clinical trials for many other pathogens such as the Ebola virus and malaria.<sup>12</sup>

It may be possible to create vaccine cocktails directed against several different pathogens by inserting multiple proteins into a single vector or by mixing several vaccines made with the same viral vector but expressing different proteins.<sup>20</sup> It is also possible to deliver the immunogenic proteins without using a replication-competent, live virus. Virus-like particles (VLPs) are self-assembling constructs that express a viral antigen, but they do not contain the necessary material to replicate. This technology was used to develop Gardasil, Merck's vaccine to protect against HPV, approved in 2006.<sup>21</sup>

In conjunction with new technology for vaccines, adjuvants are also needed. New compounds may enhance immunogenicity quantitatively, by increasing the levels of protective immune responses, and qualitatively, by eliciting responses from different arms of the immune system or by broadening the scope of covered immunogens. This advance has the potential to improve overall outcomes and achieve cost-savings by allowing lower doses to be used and, possibly, by eliminating or postponing the need for booster injections.

Although no new adjuvants have been approved in the U.S. since the original licensing of the mineral salts, several compounds appear close to being approved. The squalene-containing, oil-in-water emulsion adjuvant MF59 from Novartis has been approved in Europe for use in influenza vaccines targeted to the elderly population.<sup>22</sup> In a clinical trial in humans, another oil-in-water emulsion from GSK enhanced the immunogenicity of a potential pandemic influenza vaccine. This vaccine enabled the dose to be reduced, and it induced responses that were cross-reactive in several clades (distinct virus groupings).<sup>23</sup>

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Clinical trials of GSK's VLP-based HPV vaccine Cervarix have shown similar cross-protective responses to subtypes not included in the vaccine, which might be attributable to the novel adjuvant ASO4.<sup>21,24,25</sup> The ability of certain adjuvants to enhance the levels of memory B cells and antibodies, in some cases to numbers much higher than those seen with natural infection,<sup>26</sup> has implications for the longevity of the response as well. In one study comparing ASO4 plus alum with alum alone against HPV, significantly higher antibody titers were observed when ASO4 was included.<sup>26</sup> This advantage was maintained during long-term follow-up.

These dual benefits—extending the time that antibody levels are maintained above the threshold required for neutralization of the organism and enhancing the capacity of the patient to respond to a booster immunization—are important for future planning and estimating costs. However, we need to better define the correlates of immunity for specific vaccines. The threshold necessary for neutralization differs among various organisms; knowing this parameter and other related measures is desirable and sometimes necessary. Advances in vaccine technology necessitate concomitant advances in vaccine immunology.

Considering the rising costs of research and development, another desirable feature of adjuvants is their ability to be paired with multiple antigens so that they can be included in different vaccines. For example, ASO4 has been studied in conjunction with both hepatitis B and HPV vaccines.<sup>26</sup> This capability can reduce the vaccine's developmental costs and the time to market. With each new adjuvant and each new combination of adjuvant and vaccine, the advantages of increased immunogenicity, longevity, and perhaps broadened coverage of strains must be balanced with the potential for increased reactogenicity. In this context, reactogenicity refers to the generally undesirable effects of the vaccine, typically mediated by the immune response to the vaccine rather than by the product's direct toxicological effects. Redness or swelling at an injection site are two common examples.

Despite this rapid technical progress, vaccines were not on the "radar screen" for managed care before some of the recent product launches. Previously, the extent of managed care's involvement was limited to assisting in acquiring supplies for some integrated systems, working with quality on Health Plan Employer Data and Information Set (HEDIS) measures, and participating in clinics and health fairs. However, the advent of newer vaccines that target diseases causing morbidity rather than mortality in the U.S. (e.g., rotavirus or herpes zoster) is encouraging MCOs to perform more clinical and economic analyses in order to ensure that their investments in vaccination are being maximized.

The entry of the live attenuated influenza vaccine FluMist (MedImmune) into the market in 2004 and the anticipated introduction of a second HPV vaccine (Cervarix, GSK) present new challenges. These products target essentially the same disease processes as those targeted by vaccines already approved, but they differ in their approach and, potentially, in their clinical effectiveness. The availability of similar products is relatively new in the world of vaccines, and MCOs will have to evaluate them closely in terms of their efficacy, safety, and economic impact.

For example, the question confronting MCOs, in view of the HPV vaccine (Gardasil), as well as ASO4, and MF59, is whether the potential of lower reactogenicity from an established adjuvant is more important than the potential for a stronger and possibly more durable immunogenic response. Ultimately, we might simply derive the answer if we know which product provides better protection against the HPV types most commonly linked to cervical cancer in a cost-effective manner. These types of analyses place a greater value on cost-effectiveness, clinical, and budget-impact data for the newer vaccines—data that have been lacking in the past.

Although short-term benefits offer immediate returns to MCOs, it would be irresponsible for these health plans to focus exclusively on these benefits and deny coverage of vaccines in an effort to save money. Such restrictions place the broader population at risk, and they may have the unintended consequence of damaging a company's reputation. Further, a focus on short-term benefits puts health plans at a disadvantage in terms of competing for participants during enrollment; most plans offer broad vaccine coverage, although there might be restrictions based on product labels, guidelines, or age limitations.

Another way to increase the value of future vaccines would be to quantify both the possible short-term and long-term cost offsets attributable to the availability of the specific product. Again, because it is crucial that MCOs not waste money, the emphasis should be on outcomes and cost-effectiveness.

In concert with the advances in vaccine engineering and adjuvantation, novel routes of delivery are also being investigated.

Intradermal delivery directly to an environment rich in antigen-presenting cells (APCs) is considered to be a dose-sparing measure for several vaccines, including those used for HIV and influenza.<sup>27</sup> Needle-free variants of this route, such as transdermal patches and electroporation, are also being tested for conditions as diverse as influenza, traveler's diarrhea, and melanoma.<sup>12,28,29</sup>

Mucosal delivery, which has the advantage of not requiring a needle, is already being used for several vaccines. The live, attenuated influenza vaccine FluMist is given as a nasal spray, and the rotavirus vaccine, licensed in the U.S. in 2006, is delivered orally.<sup>30,31</sup> The mucosal route of delivery may contribute to the heterovariant cross-protection seen with both of these vaccines by inducing broader immunity, including mucosal immunoglobulin A.

Mucosal delivery is also being studied for several other potential vaccines directed against diseases such as HIV infection and tuberculosis.<sup>12</sup> In the past, MCOs tended not to pay a premium for convenience alone. If an alternative (needle-free) route of delivery is associated with improved outcomes, such a premium might be worth the additional investment.

The demand for vaccines by employers and physicians is also an important consideration. Individual health plan members and small employers might be less willing to cover the cost of new vaccines because of the possibly significant impact on premiums. Small employers with a pool of healthy young employees might not be interested in covering vaccines for disease states with poorly documented short-term benefits.

With the arrival of many new biologic agents and vaccines,

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as well as the future role of genomics, the traditional model of medical coverage may need to evolve. The questions of how these innovations will be funded and who will fund them may become more fluid.

In the past, the question of whether different vaccines created an equivalent reduction in morbidity and mortality for the same cost was not asked; however, this question needs to be addressed. Many payment and reimbursement structures—ranging from universal coverage, effective from the first dollar, to differing levels of reimbursement, such as a standard coverage (100%) versus a nonstandard benefit (a 20% plan member copayment)—will be analyzed and reviewed by those responsible for funding these advances.

Again, documented clinical and financial outcomes and targeted disease states will be playing a significant role in determining how health plans approach the placement of vaccine products. The role of activism and the Advisory Committee on Immunization Practices (ACIP) guidelines will remain important variables. This is because many health plans routinely follow the ACIP's recommendations; if this reviewing body begins to cover certain vaccines or populations, many plans will probably follow those guidelines.

### FUTURE TRENDS

The success of vaccines against childhood diseases has created enthusiasm for researching additional targets. Merck's Gardasil was the first vaccine licensed with a primary indication to prevent cervical cancer. A second HPV vaccine, Cervarix is being considered for licensure in the U.S. Other preventive cancer vaccines are also in development, many of which are in clinical trials,<sup>12</sup> and therapeutic vaccines designed to treat or ameliorate different types of cancer after it has occurred are also being pursued. Therapeutic vaccines for chronic infectious diseases such as hepatitis B, HIV, and cytomegalovirus are being studied, as are vaccines designed to halt or reverse the progression of Alzheimer's disease.<sup>12,32</sup>

Even with these new goals and with the trend of therapeutic vaccines moving toward targeting morbidity rather than mortality, we must still ask: How should efficacy be analyzed?

Although 100% efficacy is rarely seen, products with the greatest clinical impact on the broadest population have been favored. With some of the newer agents, this criterion might not remain as important. For instance, if a vaccine works in a portion of the population and that segment can be identified, an MCO might direct the product's use to ensure its appropriateness for that segment. If a screening tool or a laboratory value can narrow the pool of patients to those who are most likely to benefit from a vaccine, an MCO might use controls (e.g., prior authorizations) to ensure that the most appropriate patients are being targeted with that tool or lab value, thereby resulting in improved success and in protection of the company's financial investment.

As more costly vaccines enter the market, the financial implications for health plans and physicians will become more pronounced. The debate over who will pay and how much will be paid will only intensify. Vaccines remain the single best investment in health care,<sup>33</sup> but the costs associated with the increasing options are beginning to strain both public and private systems. Most health plans have liberal coverage and

reimbursement policies for vaccines, and this approach is considered to offer a good return on investment. As we mentioned earlier, this traditional approach may be re-examined in some areas, with many alternative options to be explored. With most of these alternatives, one goal remains: making sure that the best vaccines reach the right patients with few impediments.

For physicians, the introduction of newer vaccines has led to a greater number of nontraditional vaccinators, such as pharmacies and businesses traditionally outside the health care system that are now becoming acquainted with, and challenged by, the financial implications. Expectations about reimbursement levels and profitability may need to be addressed to ensure that all parties involved—health plans, physicians, employers, and patients—feel their contribution is significant.

In 2007, the immunization schedule for children was already crowded; 15 different vaccines were recommended for children from birth to six years of age, and 14 were recommended for older children, seven to 18 years of age. Many of these vaccines are administered multiple times, and adults may need additional boosters. The development and approval of new vaccines against infectious diseases, as well as other potential uses for them, are likely to exacerbate this problem.

A desire to simplify the regimen is fueling a trend toward combination vaccines. Although many combined vaccines have been used historically (e.g., diphtheria, pertussis, and tetanus), new combinations are being approved for children (e.g., pentavalent vaccines such as GSK's Pediarix [diphtheria, acellular pertussis, tetanus, hepatitis B, and inactivated polio vaccine]) and for adults (e.g., GSK's Twinrix for hepatitis A and B).

The main challenge will be to balance immunogenicity in the newer formulations while maintaining their benefits of easier administration and lower costs. In this regard, adherence is likely to be a key issue in the future. If it can be shown that a product improves compliance and clinical outcomes while reducing costs, that vaccine may benefit from preferential positioning by health plans.

For instance, Happe et al., using data from SelectHealth, retrospectively compared children receiving the HEDIS Combination 2 vaccine series with those receiving each vaccine series individually.<sup>34</sup> By two years of age, children in the combination cohort were more likely to have been fully vaccinated, and vaccinated within the recommended age ranges, than children receiving each series individually (86.9% vs. 74.1%,  $P < 0.001$ ; 45.2% vs. 37.5%,  $P = 0.001$  respectively). Additional studies with data indicating improved compliance rates and outcomes support the value of this technological advancement.

### COMMENTARY

Vaccines exemplify the premise behind managed care to promote wellness and prevent disease while also avoiding unnecessary treatment-related costs. The benefits of childhood vaccines in reducing mortality alone are undeniable.<sup>1</sup> However, the cost-benefit relationship for the new generation of vaccines that can target reductions in morbidity or prevent rare and costly illnesses such as cancer is less clear. The promise of a brighter future is motivation up to a point; eventually, however,

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as the health care dollar is stretched, proven results, both clinical and financial, will be required. In health care, there is an increasing awareness of the need to look at the "bigger picture" and to have less "silos" between pharmacy and medical divisions. Most organizations that practice evidence-based medicine acknowledge that both pharmacy and medical dollars often need to be spent in order to realize improved overall outcomes and reduced long-term expenses.

One obstacle that affects this "investment" is the phenomenon of continuous enrollment in areas of the community with high competition for plan enrollees. If one plan invests liberally in vaccine benefits but a competitor does not, is the plan making the investment placed at a disadvantage in terms of premiums? Community-wide standards, agreed upon by health plans, employers, and physicians, would need to address this matter and ensure that all parties act in concert through their investments in the short-term and long-term health of the community.

Rapid advances in our understanding of the immune system and our desire to engineer both preventive and therapeutic vaccines for a wide spectrum of diseases are fueling changes in medicine and in the managed care industry. There will be a growing emphasis on providing evidence-based medicine demonstrating tangible, long-term clinical benefits and cost effectiveness. There will always be a need to balance cost, efficacy, and choice, and our advancements in science will force all parties to alter their approaches to treatment.

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